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LOCAL AND WIDESPREAD HYPERALGESIA AFTER ISOLATED TIBIAL SHAFT FRACTURES TREATED WITH INTRAMEDULLARY NAILING

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Running head: Pain after tibial shaft fracture

Keywords: pain, pain sensitivity, tibial shaft fracture, intramedullary nailing

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ABSTRACT

Objectives: Knee pain is accepted as a common complication to intramedullary nailing of tibial fractures. However, no studies have systematically studied the pain sequel following tibial fractures. The objective of this study was to assess pain and hyperalgesia from 6 weeks to 12 months postoperatively after intramedullary nailing of an isolated tibial shaft fracture.

Methods: A total of 39 patients were included in this 12-month follow-up study. After 6 weeks, 3, 6 and 12 months postoperatively the pain intensity was measured on a visual analogue scale (VAS) and the pressure pain sensitivity was assessed bilaterally by pain pressure thresholds (PPTs).

Results: The mean age at the time of fracture was 42.9 years. Twelve months after surgery the pain intensity for worst pain during the last 24 hours was 1.8±2.7 cm. The PPTs progressively increased from 6 weeks after surgery to 12 months postoperatively for all PPT sites except for the forearm ($P < 0.012$). Moreover, the PPTs on the leg were generally reduced on the injured side compared with the non-injured side ($P < 0.04$).

Conclusions: This study suggests that localized, distal and bilateral hyperalgesia are common following an isolated tibial shaft fracture treated with intramedullary nailing, although no widespread (extrasegmental) hyperalgesia was detected. Such observations may be important for developing the most adequate rehabilitation procedure following a tibial fracture.

Keywords: tibia fracture, pain sensitivity, hyperalgesia

INTRODUCTION

Knee pain is accepted as a common complication to intramedullary nailing of tibial shaft fractures[1-4]. Keating et al. [4] reported, with a mean follow-up period of 32 months postoperatively, knee pain in 57% (63 out of 110 knees) of patients after intramedullary nailing of the tibia. A recent study by Larsen et al. [3] reported a 44% higher incidence of knee-related pain compared to an established reference population in a group of 223 patients treated with intramedullary nailing following a shaft fracture of the tibia. Although pain is generally accepted as a common complication, no previous studies have systematically studied the pain sequel and hyperalgesia in patients following a tibial shaft fracture treated with intramedullary nailing.

The trauma leading to a fracture of the tibia with the corresponding tissue and muscle damage may lead to pain sensitization such as widespread hyperalgesia[5]. So far no studies have systematically studied the pain sequel following intramedullary nailing of tibial shaft fractures and whether local or widespread hyperalgesia is present in these patients. Studies have reported knee pain to be worse in women following tibial shaft fractures[3,6] and such findings are in line with the generally higher frequency of musculoskeletal pain in women[7].

Assessment of local and widespread deep tissue pain sensitivity by recording of pain pressure thresholds (PPTs) has been used in numerous studies on patient groups with musculoskeletal pain[5,8-10]. It has been demonstrated that a tissue insult is associated with reduced pain pressure thresholds[5] and that patients with chronic musculoskeletal pain reported more deep tissue hyperalgesia[9,11,12]. A systematic review by Suokas et al. [11] reported that patients with knee osteoarthritis presented with lower PPTs than healthy controls in general and that both the affected joint and the remote side were affected.

The objective of this study was to investigate the development of pain and hyperalgesia from 6 weeks to 12 months postoperatively after intramedullary nailing of an isolated tibial shaft fracture. The secondary aim was to analyze whether gender or bone healing status affects pain and hyperalgesia.

METHODS AND MATERIAL

Material

All patients treated with intramedullary nailing after an isolated tibial shaft fracture with or without a fracture of the fibula bone between September 2012 and April 2014 at Aalborg University Hospital, Denmark, were included in the study. Patients with tibial shaft fractures treated without intramedullary nailing, patients with bilateral fractures and patients with pathological fractures were excluded. Patients who were unable to participate due to mental disabilities were excluded. Information about age, gender, trauma mechanism, type of trauma, fracture classification, type of surgery, complications and the development of pain was registered. All participants gave written informed consent at the time of admission to hospital. The study was approved by the Danish Data Protection Agency (J. nr. 2008-58-0028) and the local ethics committee (J.nr: N-201-200-11), and performed according to the principles of the Helsinki declaration.

Study design

The study design was a prospective follow-up study including all patients treated with intramedullary nailing after an isolated tibial shaft fracture. The primary outcome measurement was the pain pressure threshold (PPT). Patients' baseline characteristics were obtained at the time of admission to hospital.

All patients treated with intramedullary nailing following a tibial shaft fracture in our level 1 Trauma center, is treated within a standard guideline from the time of fracture to 12 months post-operatively. The guideline includes instruction on operative technique, per- and post-operative analgesia and post-operative rehabilitation. Six weeks after surgery, all patients were referred to three months standardized physiotherapy rehabilitation. All patients were systematically examined at the outpatient clinic after 6 weeks, 3 months, 6 months and 12 months.

Pain intensity

The pain intensity of the injured leg for worst pain during the last 24 hours and rest pain was measured on a 10 cm visual analogue scale (VAS) with the endpoints “no pain” and “maximal pain.”

Pressure pain sensitivity

The pain sensitivity was assessed by pressure pain thresholds (PPTs) recorded by handheld pressure algometry (Algometer Type II, Somedic AB, Sweden). Pressure was applied at a rate of 30 kPa/s with a 1 cm^2 probe until the patient perceived the pressure as painful and pressed the stop button. The rate of increase in pressure was kept by using a scale on the pressure algometry indicating the rate of change in pressure. The assessor ensured that the scale indicated approximately 30 kPa/s during assessment of PPTs. If the test exceeded 1000 kPa it was interrupted and 1000 kPa was documented as the test result. The PPT was assessed bilaterally at 6 sites in the knee region and 1 site on the forearm (Figure 1). All PPT assessment sites were assessed twice and each recording was separated by approximately 5 seconds. The average of two PPT measurements from all 7 sites, respectively, was calculated and used for further analysis.

Radiological outcome measurements

Radiological examinations were performed at 6 weeks, 3 months, 6 months and 12 months postoperative. Fracture classification was carried out according to the Orthopedic Trauma Association Classification (AO) [13] and was conducted on the preoperative X-rays.

Evaluation of fracture union and alignment was based on postoperatively X-rays of the fractured lower leg and clinical examination of the fracture site. The radiological assessments were made on AP and side X-rays. The evaluation of union were defined as: *i*) visible callus formation on at least three of four sides, no visible fracture line and no pain from fracture at weight-bearing and following clinical examination (defined as: union), *ii*) visible callus formation on at least 1 of 4 sides, with a visible fracture line (defined as: partial union) and *iii*) visible fracture lines and no visible callus formation (defined as: no union). The evaluation of union was performed in agreement with other studies evaluation union after tibial fractures[14]. Two authors carried out radiological evaluations separately (PL & RE). In cases of disagreement, consensus was obtained.

Statistics

The assumption of normal distribution variables was checked visually by QQ-plots. Continuous data were expressed as mean and standard deviation (SD). Categorical data were expressed as frequencies.

A 2-way mixed-model repeated measures analysis of variance (RM-MX-

ANOVA) was used for the analysis of the differences in PPTs between the factors *time* (6 weeks, 3, 6 and 12 months postoperatively) and *leg* (non-injured and injured leg). If significant factors or interactions were found, post-hoc analyses with Bonferroni corrections were used. A 2-way mixed-model repeated measures analysis of variance (RM-MX-ANOVA) was used to test the difference in PPTs at the injured leg related to gender difference and whether the fracture was united or not. Spearman's rank test was used for analysis of the correlation between VAS pain and PPTs.

A P-value of < 0.05 was considered significant. The statistical analysis was performed using SPSS (version 22).

RESULTS

A total of 40 patients were treated for an isolated tibial shaft facture with intramedullary nailing during the study period. One patient was initially excluded due to a pathological fracture and at the final follow-up after 12 months, 35 patients (14 women) completed the examination. The mean age at the time of the fracture was 42.9 years, ranging from 18 to 79 years. The baseline characteristics of all patients concerning trauma mechanism, type of trauma, fracture classification, open or closed fracture and complications due to treatment are presented in Table 1. The majority of patients presented with a closed diaphyseal simple shaft fracture of the tibia (AO-type 42 A-), with additional fracture of the fibula. All fractures were united within 12 months.

At the time of referral of the hospital all patients were offered analgesia in the form of paracetamol and morphine. At the 6 weeks follow-up, only 5 patients were still using analgesia.

Pain intensity

At the final examination 12 months after surgery the VAS score for worst pain during the last 24 hours was reported with a range from 0 to 10 cm with an average of 1.8 ±2.7 cm. Eighteen patients reported no pain, 14 patients reported VAS between 1 and 5 cm and 3 patients reported VAS between 6 and 10 cm. The VAS score for resting pain at 12 months follow-up was reported with a range from 0 to 5 cm with an average of 0.5 ±1.3 cm. Twenty-five patients reported no pain at rest and 10 patients reported VAS between 1 and 5.

Figure 2 shows the development of pain from 6 weeks after surgery to 12 months postoperatively in patients reporting VAS scores grouped by VAS 0, 1–5 and 6–10 for worst pain during the last 24 hours.

Postoperative development of pressure pain sensitivity

Table 2 shows the development of outcomes for PPT measurements from 6 weeks after surgery to 12 months postoperatively for the injured and the non-injured leg.

The repeated measures analysis mixed-model ANOVAs used for individual PPT sites at all time points and the injured and non-inured leg showed a substantial main effect for time at all PPT sites except from the forearm (RM-MX-ANOVA: $F_{3,108} > 3.9$, $P < 0.012$) showing an overall progressive increase in PPTs between the 6-week and the 12-month time points in both legs. The post-hoc comparisons of the 4 time points postoperatively showed a significant increase in PPTs between 6 weeks and 12 months for PPT sites 1, 3 and 5 ($P > 0.032$). PPT sites 1 and 5 showed a significant increase in PPTs between 3 months and 12 months ($P > 0.012$). The PPTs at site 1 and 5 were significantly increased between 6 weeks and 6 months ($P > 0.03$).

Significant main effects were found between the injured and non-injured leg at all PPT sites except from site 7 at the forearm (RM-MX-ANOVA: $F_{1,34} > 4.7$, $P < 0.04$). The post-hoc test showed significantly reduced PPTs (site 1-6) in the injured leg compared with the non-injured leg at every time points ($P < 0.04$) except for the PPTs recorded at sites 1-7 after 12 months ($p > 0.062$).

Pressure pain sensitivity of the injured leg between genders

The 2 way RM-MX-ANOVAs of PPT sites 1-7 and genders showed a significant difference between genders for all PPT sites at the injured leg (RM-MX-ANOVA: $F_{1,34} > 15.6$, $P < 0.006$). The post-hoc test showed significantly reduced PPTs (site 1-7) in females compared to men at every time points ($P < 0.003$)

In the injured leg, the relative PPT changes over time at sites 1–6 and forearm showed no significant difference between females and males (RM-MX-ANOVA: $F_{1,34} > 1.3$, $P > 0.262$) indicating that it could not be demonstrated that women following a tibial shaft fracture experience a relative higher increase in PPTs compared to men.

Pressure pain sensitivity in relation to fracture status and pain intensity

At the time points 3 and 6 months postoperatively the analysis of PPT sites 1–7 showed no significant difference between the patients who presented with a united fracture and those whose fractures had not united (RM-MX-ANOVA: $F_{1,34} > 2.4$, $P < 0.706$) indicating that fracture union was not associated to the level of hyperalgesia following a tibial shaft fracture. At 12 months after surgery all fractures had united.

Correlations between pressure pain thresholds and pain intensity

At the time points 6 weeks, 3, 6 and 12 months after surgery no statistically significant correlations between individual VAS scores (worst pain during the last 24 hours) and mean PPT level (averaged data from sites 1–6 of the injured leg) were found (Spearman's rank test: $R > 0.141$, $P < 0.404$). The relationship between individual VAS scores (worst pain during the last 24 hours) and PPTs on the forearm (site 7) at the four time points postoperatively showed no statistically significant correlations (Spearman's rank test: $R > -0.102$, $P < 0.564$).

DISCUSSION

This is the first study to examine pain reaction and hyperalgesia in patients following a tibial shaft fracture treated with intramedullary nailing, from 6 weeks after surgery until 12 months after fracture. The main outcome of this study was the observation of a decreased level of mechanical pain threshold in the injured leg compared to the non-injured leg at all time points postoperatively and a bilateral equal level of mechanical pain pressure within 12 months.

The change in PPTs in both the injured and non-injured leg in the study period may indicate that localized, distal and bilateral hyperalgesia after tibial shaft fractures is common, although no conclusion can be directly drawn in the absence of a pre-injury level of PPTs. Moreover, no changes were observed for the PPTs measured at the forearm, suggesting that the possible presence of distal and widespread hyperalgesia in the lower extremity was not part of a generalized sensitization in the patient group. These findings are novel, and no other studies have systematically evaluated pain reactions from the time of surgery and onwards following a tibial shaft fracture.

Knee pain after intramedullary nailing of a tibial shaft fracture is reported as a common complication[2-4,15]. The present study suggests that not only is knee pain a common complication after tibial shaft fractures but also a combination of localized, distal and bilateral widespread hyperalgesia is common within the first 12 months postoperatively.

The observed altered PPT during the 12 months in both legs may be explained by lower PPTs after injury, which is becoming normalized. But as no data from healthy participants are included, no unequivocal conclusion can be drawn on the causality. In agreement with the findings of the present study, previous studies evaluating other musculoskeletal disorders have reported bilateral decreased PPT levels and widespread hyperalgesia[8]. The reason for these findings may be a central segmental sensitization or alternatively simple overuse in the non-injured leg, but no studies have demonstrated this.

This study showed that females presented with lower PPT levels than men. These findings are supported by a number of recent studies reporting lower mechanical pressure levels in females with musculoskeletal injuries[7,16].

Studies evaluating outcomes after tibial shaft fractures have reported that women in general reported worse outcomes than men after tibial shaft fractures[3,6]. These findings could be reflected in more pressure pain hyperalgesia in women following a tibial fracture, but the present study showed no development in PPT levels at the forearm throughout the time period postoperatively. An analysis of the relative difference between PPT levels at the injured leg and the forearm showed no statistically significant gender difference; an indication that women following a tibial shaft fracture do not experience a relative increase in hyperalgesia compared to men.

The analysis of PPT levels and whether or not the fracture had united did not show a significant difference between the groups after 3 and 6 months postoperatively.

After 12 months all fractures had united. The general understanding is that a relationship between pain and fracture movement exists, however this understanding lacks evidence.

The present study did not show correlations between VAS and PPT levels, indicating that increased hyperalgesia was not associated with increased pain following a fracture of the tibia. However, Arendt-Nielsen et al. [12] reported statistically significant correlations between individual VAS pain and PPTs in patients with painful knee osteoarthritis. This difference may be due to the relatively short time period and acute onset of pain following an injury such as a fracture of the tibia. Patients with knee osteoarthritis presenting with chronic and progressive disability and, as a consequence, pain, which has often been present for a considerable amount of time, and with high VAS pain scores, are common[12,17].

For rehabilitation after intramedullary nailing of shaft fractures a wide range of interventions, from passive to active exercise, joint mobility, muscle strength and functional training, has been used[18,19] with a lack of scientific evidence. Findings from the present study suggest that localized and bilateral hyperalgesia after tibial shaft fractures are common within 12 months postoperatively, and clinicians should take this information into consideration when planning rehabilitation programs.

The observational follow-up design and the lack of a control group are the main limitations of the present study, implying that no conclusions regarding causality can be drawn from this study. However, the study provided novel findings and useful clinical relevant hypotheses relevant for future trials. Finally, the result of the present study is based on a study population from a single centre, with a few surgeons and only one type of intramedullary nail, which may have caused a potential selection bias, indicating that extrapolation on the conclusions may be biased and more research is needed. Moreover, the measurement error associated with repeated PPT testing of sites at the lower extremity has been reported in the literature [20,21], but no studies are conducted on patients following a fracture of the lower extremity.

Conclusion

The findings from the present study suggest that localized, distal and bilateral hyperalgesia are common following an isolated tibial shaft fracture treated with intramedullary nailing. No changes were observed for the PPTs measured at the forearm, suggesting that the observed distal and widespread hyperalgesia in the lower extremity were not part of a generalized sensitization in the patient group.

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Figure legends:

Figure 1: Locations of pressure pain thresholds on the lower extremity.1. 2 cm distally to the inferior lateral edge of the patella. 2. 2 cm distally to the inferior medial edge of the patella. 3. Center of the patella. 4. 2 cm proximally to the superior edge and the patella. 5. M. vastus medialis. 6. M. tibialis anterior. (5 cm. distally of the tibial tuberosity). 7. M. extensor carpi radialis longus (5 cm. distally to the lateral epicondyle of the humerus; not illustrated)

Figure 2: Patient reported worst pain during the last 24 hours, divided into groups of VAS = 0, VAS between 1 and 5 and VAS between 6 and 10 at time points 6 weeks, 3, 6, 12 months.

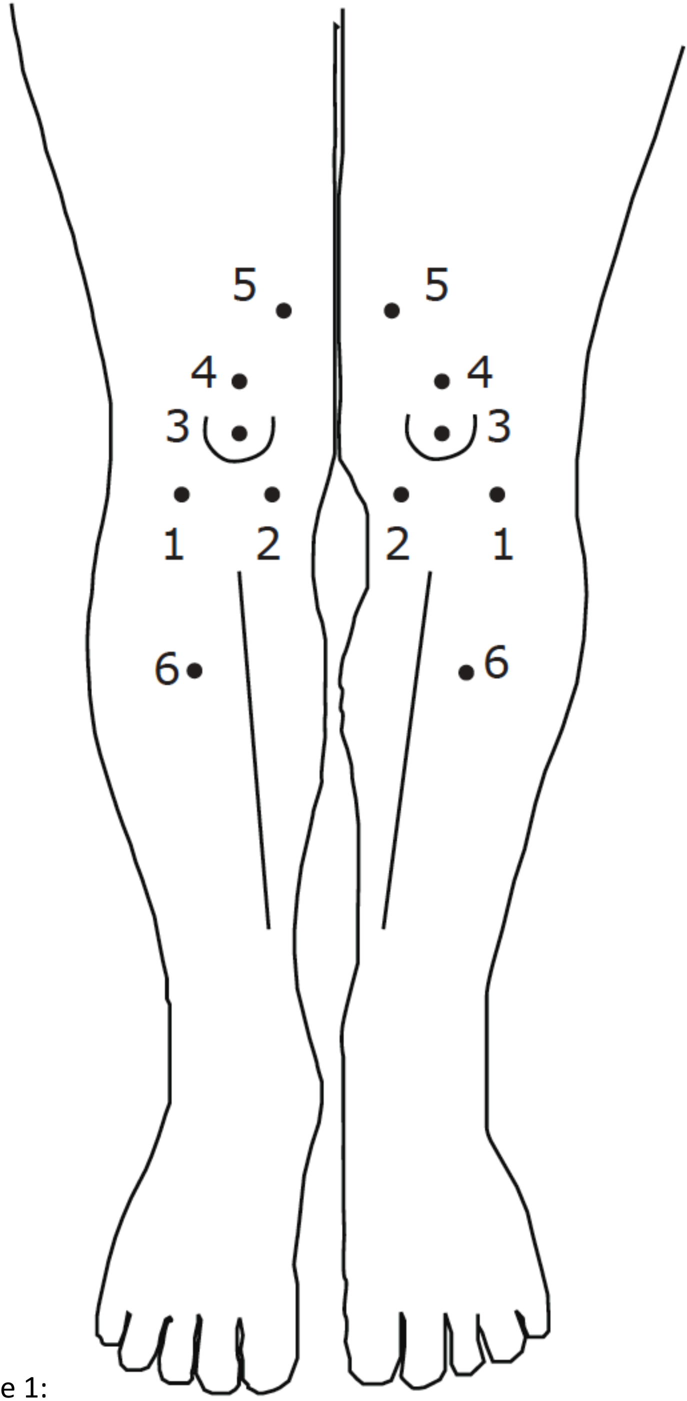

Figure 1:

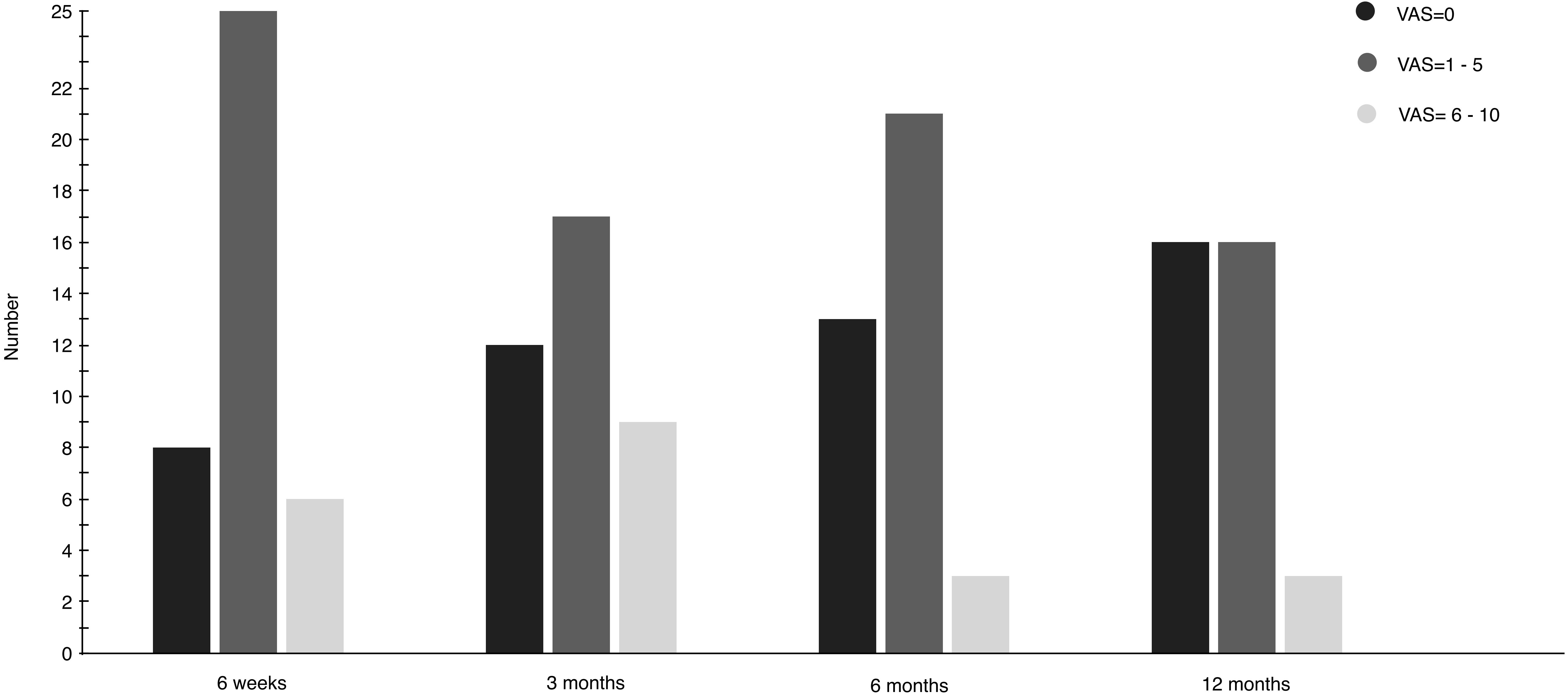

Figure 2

Pain after tibial shaft fracture

Table 1: Baseline characteristics of the 39 patients

Age at time of fracture, mean (range)	42.9(18-79)
Gender, male/female	24/15
Height, mean (SD)	175.9 (11.8)
Weight, mean (SD)	77.6 (14.6)
BMI, mean (SD)	25.1 (3.7)
Smoker, yes/No	15/24
High/low-energy trauma	10/29
Fracture classification AO-42-	
A	
B	25
C	10
Open/closed fracture	5/34
Fibula fracture, no/yes	3/36
Additional tratment besides intramedullary nailing	
Screw fixation of the posterior aspect of the tibia	9
Matatarsfracture treated with Kirschner-wire	1
Complications	
Compartment syndrome	1
Broken screws	1
Preinjury medical history	
ACL and meniscus injury	1
Radiological signs of osteoarthritis (Kellgren & Lawrence grade >=3)	1

Table 1:

Developement of PPT measurements from 6 weeks after surgery to 12 months post operatively

		6 weeks			3 months			6 months			12 months		
Site	Leg	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
	Injured	412.4	220.6	37.8	426.5	219.8	36.6	509.3	237.1	38.9	540.4	271.9	46.6
PPT 1 *, **	Non-injured	487.1	252.5	43.3	501.9	245.9	41.0	541.9	243.1	39.9	576.6	273.8	46.9
	Injured	346.5	208.9	35.8	341.2	191.2	31.8	403.1	203.9	33.5	415.5	248.1	42.6
PPT2	Non-injured	401.7	199.6	34.2	433.8	211.9	35.3	432.5	237.3	39.0	473.2	241.9	41.5
	Injured	376.8	194.1	33.3	390.9	189.4	31.6	469.7	195.0	32.1	527.3	261.9	44.9
PPT3 *	Non-injured	467.1	204.7	35.1	474.5	206.4	34.4	477.1	207.8	34.2	551.3	257.6	44.2
	Injured	532.7	227.5	39.0	549.9	237.7	39.6	589.8	228.9	37.6	602.2	240.6	41.3
PPT4	Non-injured	611.7	242.6	41.6	598.9	235.7	39.3	612.9	247.4	40.7	662.0	252.5	43.3
	Injured	425.2	220.2	37.8	442.3	210.9	35.2	511.1	205.6	33.8	553.1	249.9	42.9
PPT5 *, **	Non-injured	472.4	243.1	41.7	482.6	198.4	33.1	537.9	223.4	36.7	591.9	264.8	45.4
	Injured	439.5	225.6	38.7	473.1	216.0	36.0	495.4	209.0	34.4	540.1	251.1	43.1
PPT6	Non-injured	511.6	261.4	35.5	521.2	244.6	40.8	548.9	243.5	40.0	578.5	258.7	44.4
	Injured	345.7	204.8	35.1	334.2	186.5	31.1	370.5	201.0	33.0	372.2	203.3	34.9
PPT7	Non-injured	366.3	207.1	35.5	336.2	194.9	32.5	384.5	212.6	34.9	369.3	201.0	34.5

SD=standard deviation, SEM=standard error of the mean

* Significant increase in PPTs between 6 weeks and 12 months

** Significant increase in PPTs between 6 weeks and 12 months and 3 months and 12 months

Table 2